The Field Studies and Statistics Program

Fiscal Year 1980

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

REPORT OF THE

FIELD STUDIES AND STATISTICS PROGRAM

Fiscal Year 1980

National Cancer Institute
Division of Cancer Cause and Prevention

NIH Publication No. 81-2311

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health

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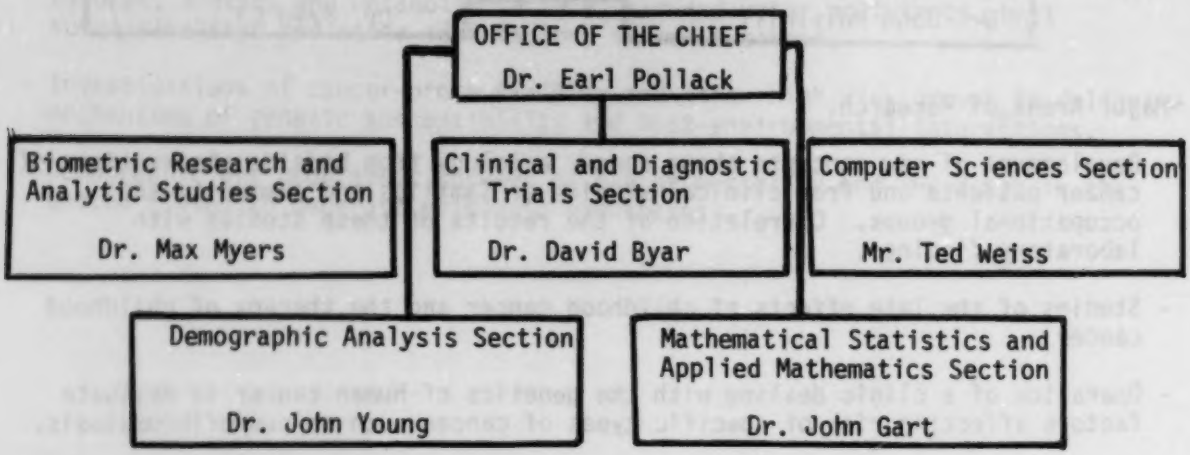
FIELD STUDIES AND STATISTICS PROGRAM

Office of the Associate Director .... Dr. Joseph F. Fraumeni, Jr., Acting

Administrative Officer ..... Ms. Colleen Sherwood

BIOMETRY BRANCH



Major Areas of Research:

- Measurement and detailed analysis of cancer incidence, mortality and patient survival through a series of population-based cancer registries covering 10 percent of the U. S. population.
- Design and conduct of randomized clinical trials and development of associate basic statistical methodology and theory.
- Design and conduct analytic studies of suspected factors associated with the risk of developing cancer.
- Development of statistical methodology for a wide variety of laboratory experiments. Application of complex data analytical methods to specific problems.
- Development of mathematical models which attempt to explain basic processes of carcinogenesis.
- Design and analysis of studies involving screening for cancer in populations and development of associated statistical theory.
- Development of computer technology appropriate for large-scale cancer patient reporting systems.

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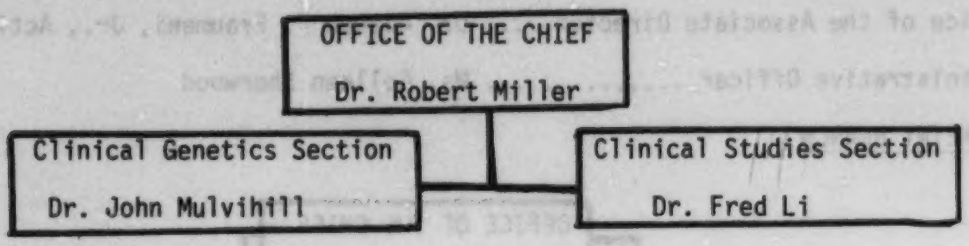
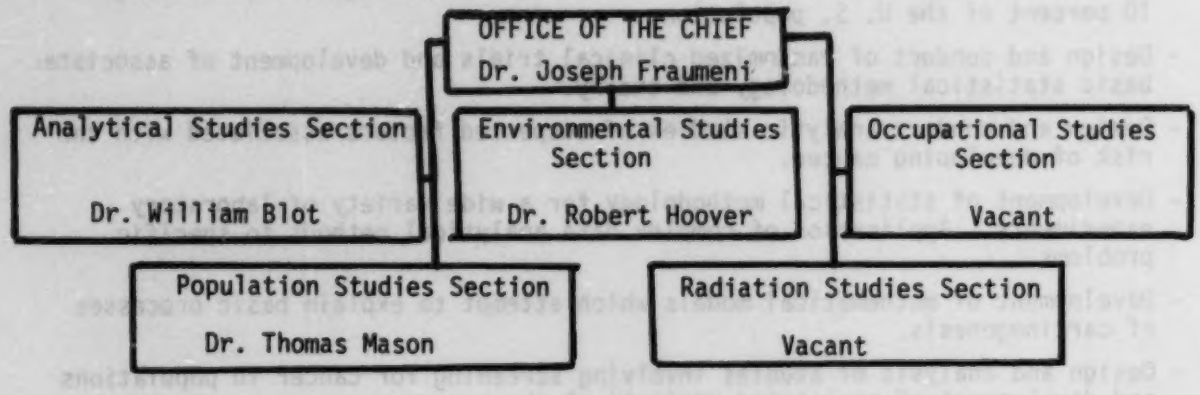
CLINICAL EPIDEMIOLOGY BRANCH



Major Areas of Research:

- Development of new concepts about cancer etiology from bedside observations of cancer patients and from clinical studies of families and community and occupational groups. Correlation of the results of these studies with laboratory findings.
- Studies of the late effects of childhood cancer and the therapy of childhood cancer.
- Operation of a clinic dealing with the genetics of human cancer to evaluate factors affecting risk of specific types of cancer such as neurofibromatosis.
- Preparation of analytical reviews to define current status and future prospects for research in specific areas of clinical epidemiology.

ENVIRONMENTAL EPIDEMIOLOGY BRANCH



Major Areas of Research:

- Epidemiologic studies of selected occupational groups to help identify chemical and physical carcinogens.
- Epidemiologic studies of radiation-exposed groups, in order to clarify the effects of low-level exposure.
- Epidemiologic studies to evaluate the effects of exogenous hormones, immunosuppressive and cytotoxic agents, and other drugs suspected of being carcinogenic.

- Epidemiologic studies to clarify the role of dietary fat, fiber, micronutrients, food additives, and other nutritional factors in cancer etiology.

- Case-control studies of particular cancers to pursue key etiologic leads, and to determine reasons for geographic peculiarities in the United States.

- Multidisciplinary studies utilizing laboratory measures to evaluate candidate viruses, dietary and metabolic factors, air and water pollutants, host susceptibility, and other risk factors in human cancer.

- Investigations of cancer-prone families and other high risk groups to delineate mechanisms of genetic susceptibility and host-environmental interactions.

- Demographic and geographic surveys of cancer mortality and incidence in the United States to generate etiologic hypotheses.

REPORT
FIELD STUDIES AND STATISTICS PROGRAM
October 1, 1979 through September 30, 1980

In December 1979, Dr. Joseph F. Fraumeni, Jr. was appointed Acting Associate Director for Field Studies and Statistics in the Division of Cancer Cause and Prevention. This program area consists at present of the Biometry Branch (Chief, Dr. Earl S. Pollack), the Clinical Epidemiology Branch (Chief, Dr. Robert W. Miller), and the Environmental Epidemiology Branch (Chief, Dr. Joseph F. Fraumeni, Jr.). In summary reports the Branch Chiefs have outlined the research activities under their direction. In this report the orientation of the overall FS&S program is summarized and discussed in terms of new challenges and future directions.

Mission

It is difficult to project activities over time, given the uncertainties related to a proposed NCI reorganization, available positions, funds, manpower, and especially the direction that new leads and opportunities will take. However, the objective of FS&S is to attain a comprehensive, flexible and balanced program that will enhance our capacity at the national level to generate fresh ideas and help settle key questions in cancer epidemiology and biometry. Toward this end, a selective expansion and reorientation of the program seems warranted to augment existing project areas, initiate new lines of research, and make the most efficient use of resources located at NCI and several federal agencies. Although its primary responsibility is intramural research, FS&S has a clear obligation to provide biometric and epidemiologic support to all parts of the National Cancer Program, to foster parallel efforts throughout the cancer program, and to promote epidemiology training opportunities at NIH and elsewhere.

With mounting interest in environmental cancer and in the contributions to etiology and prevention that can be made through the epidemiologic approach, FS&S has been asked to increase the scope of its work and to help shape federal programs and policy in several areas. Despite substantial growth and support of the epidemiology program over the past four years, there are still insufficient senior staff to keep pace with the opportunities and demands for research and consultation in the field of environmental cancer. Furthermore, FS&S contributes not only to cancer etiology, but also to natural history, end results, clinical trials, preventive measures, and even strategies involved in administrative planning and decision-making. Epidemiologic and biometric approaches permeate many aspects of the National Cancer Program, and are fundamental to the design and evaluation of methods to control cancer. This entails close interaction and coordination between personnel in FS&S and throughout the Institute.

Demography

A major objective of FS&S is to generate national statistics on cancer incidence, mortality and survival. This provides valuable signals

for further epidemiologic study, and for monitoring the progress of the National Cancer Program. The Surveillance, Epidemiology and End Results (SEER) program has collected population-based statistics on cancer incidence and patient survival since 1973, covering about ten percent of the U.S. population. There will soon be detailed reports of this experience and a characterization of the ethnic and socioeconomic influences on cancer incidence and survival. A subcommittee of the Board of Scientific Counselors of DCCP was recently appointed to review the SEER program and will recommend changes to promote productivity, efficiency, and economy. Since non-melanoma skin cancer is not covered by the cancer registries, a special incidence survey will be completed in various areas around the country. In the past, a county-by-county survey of cancer mortality in the United States (1950-69) has identified geographic clusters of elevated rates that provide etiologic clues and opportunities for further study. New maps are being prepared to cover cancer mortality in the recent time period 1970-75, and to illustrate the geographic patterns for non-neoplastic disorders that may be etiologically related to cancer.

Analytic Epidemiology

Further development of FS&S is needed to strengthen our program of case-control and cohort studies in the following areas. 1) Occupational studies are a valuable means of identifying chemical and physical carcinogens, and will be expanded to assess the many hazards suggested by experimental and clinical observations. 2) Radiation studies require more emphasis as pressure mounts to clarify the effects of low-level exposures and the shape of the dose-response curve. Studies of A-bomb survivors will be pursued by cooperative arrangements with the Radiation Effects Research Foundation in Japan. 3) Drug studies will be expanded to evaluate the effects of estrogenic compounds, immunosuppressive and cytotoxic agents, and other agents suspected to have carcinogenic activity. 4) Nutritional studies will be intensified to clarify the role of dietary fat, fiber, micronutrients, and food additives in cancer etiology. A focus of study will be migrant groups and other U.S. populations where cancer risk may have been altered by changing dietary habits. 5) Family studies have been enhanced by the development of a computer-based data resource, and should result in a more precise delineation of family cancer syndromes, such as the dysplastic nevus syndrome that predisposes to familial melanoma. 6) Case-control studies of selected cancers will be pursued vigorously, either when high-risk communities are identified on the cancer maps, or when testable hypotheses and special resources become available. Whenever appropriate, the studies will involve collaboration with federal and state agencies, SEER registries and cancer centers, military hospitals, record-linkage systems, and the like. 7) Environmental pollutants, such as water contaminants, agricultural chemicals, and air pollutants, will be evaluated through these studies by integrating appropriate environmental and body measurements. 8) Multidisciplinary projects combining epidemiologic and experimental approaches will be encouraged to evaluate candidate viruses, dietary and metabolic factors, host susceptibility, air and water pollutants, and other causative factors that may continue to elude detection by traditional observational methods.

Biometrics

The development of statistical methodology in FS&S contributes greatly to several areas, including epidemiology, carcinogenesis research, therapy trials, and screening programs. Efforts are underway to increase and structure investigative work in the screening and early detection of cancer. Development of a screening methodology group in FS&S would help fill a gap area in NCI, and assist the Division of Cancer Control and Rehabilitation in designing, monitoring and evaluating the extramural screening programs. This may be accomplished through a close working relationship between FS&S biometricians/ epidemiologists involved in screening methods and the appropriate DCCR staff. More biostatistical work is also needed in the field of carcinogenesis, including the development and testing of multi-cause and multi-stage models, and the clarification of issues involved in extrapolating results from animal experiments to man.

Collaboration

Collaborative studies with other federal agencies will be given high priority to 1) evaluate urgent issues including those of immediate regulatory or public policy concern, and 2) stimulate the epidemiologic application of technical and data resources that are used by the government primarily for other purposes. Many research and regulatory agencies are concerned with environmental cancer, yet few have epidemiologic programs, and require assistance and support on many issues. Particularly at this time of fiscal restraint, it is important to increase initiatives to develop and coordinate national data resources that, with appropriate safeguards, may be tapped by qualified investigators throughout the country. The FS&S will also work closely with other groups in efforts to remove the serious obstacles to epidemiologic research resulting from proposed extensions of the privacy and confidentiality laws and by the excessive delays and complexities created by proposed OMB clearance procedures. The bi-national programs offer major epidemiologic opportunities for international studies, and next year special emphasis will be given to joint studies and exchange programs with Chinese scientists to pursue clues drawn from the recent county-based maps in China. Within the NCI further steps will be taken to improve communication and coordination of epidemiology and biometry programs, and to stimulate multidisciplinary activities linking epidemiologists with experimentalists and clinicians.

REPORT
BIOMETRY BRANCH
October 1, 1979 through September 30, 1980

The major functions of the Biometry Branch are: to measure trends in cancer incidence and patient survival over time and to assess differences in these measures among important population subgroups; to conduct research on the etiology of cancer in man; to develop statistical methodology applicable to clinical trials and other follow-up studies as well as to other problems in cancer research; and to provide statistical and computer science support to other research investigators outside the Branch. This work is accomplished through in-house studies and through field studies, some of which are carried out collaboratively with investigators in this country and abroad. The program is summarized briefly below.

Surveillance, Epidemiology and End Results (SEER) Program

The SEER Program, which is operated primarily by Dr. John Young and his Demographic Analysis Section, obtains cancer incidence and patient survival data through a group of eleven population-based cancer registries covering all cancers diagnosed in the populations of five entire states (Connecticut, Hawaii, Iowa, New Mexico, and Utah), five metropolitan areas (Atlanta, Detroit, New Orleans, San Francisco, and Seattle) and the Commonwealth of Puerto Rico. The first report on cancer incidence and mortality, covering this entire program, was published in October 1978. A monograph of over 1,000 pages presenting detailed data, area by area, for the period 1973-1977 has been submitted for publication. Thus, a set of basic data will be available to cancer researchers as well as to those concerned with various aspects of the cancer problem.

Data have been reported by all of the cancer registries for the time since their entry into the program through the end of 1978. There is evidence that the 1978 data are not yet complete but the missing data will be supplied in August 1980.

Meanwhile the data for 1973-1977 have been used to make comparisons among the various ethnic groups within the eleven SEER area populations. When ranked by incidence rates per 100,000 population for all sites combined, both Hawaiian males (465.0) and Hawaiian females (408.5) had the highest rates in their respective sex groups. Among the males, Blacks (454.3) were second and Whites (371.6) third while among females, Whites (301.2) were second and Blacks (288.7) third. For individual sites, however, the picture varied considerably. The Hawaiians in Hawaii and the Hawaii-Japanese had by far the highest stomach cancer rates among males (51.4 and 47.3 respectively) and the Whites had the lowest (12.7). For colon cancer among males, on the other hand, the rates were highest among six groups (ranging from 34.3 to 39.6) -- Whites, Blacks, San Francisco-Chinese, Hawaii-Chinese, San Francisco-Japanese and Hawaii-Japanese. The lung cancer rates were highest among Hawaiians for both males and females (116.9 and 50.7 respectively). They were next highest among Black males (110.0) and White males (76.4). Among females, lung cancer incidence was also relatively high among the San Francisco-Chinese (33.1) and the Hawaii-Chinese (29.8). Examination of the primary site distribution for each ethnic

group reveals that for males, among the Blacks, Hawaiian and Whites, lung was the most frequent site of cancer. Among the Japanese, Chinese, and Filipinos, colon and rectum was the leading site and among the Puerto Rican-Spanish, the New Mexico-Spanish and the American Indian, prostate was the most frequent site. For females, breast was the most frequent site for every ethnic group, but for the American Indian cervix was equally as frequent, with gall bladder following closely behind. Analysis of these data for ethnic groups in detail provide a basis for the formulation of specific hypotheses for further study.

Trends in cancer incidence and differences across geographic areas are also being analyzed in detail.

Clinical and Diagnostic Trials

During the year Dr. Byar and members of his section have been involved in the continuation of a number of studies and in the initiation of several new ones. This section serves as the statistical coordinating center for some of the major clinical trials. This includes the development of the detailed study plans, randomization of patients, collection, processing, editing and analysis of the data and preparation of scientific papers. In the course of this work and as an outgrowth of consultation on other studies, this group has been very active in the development of statistical methodology that has application particularly in the areas of clinical trials and epidemiologic research. A brief summary of some of the major activities is as follows:

1) Analysis has continued on the data on over 4,000 patients with prostate cancer that were obtained from the randomized clinical trials conducted by the Veterans Administration Cooperative Urological Research Group between 1960 and 1975. A number of questions were addressed using this data set.

2) The Inter-group Study of Testicular Cancer, a nationwide randomized trial, comparing adjuvant combination chemotherapy following surgery for resectable stage II disease versus chemotherapy only for relapses was implemented during the year. Patient accrual is continuing and initial processing of the data has begun.

3) Data on some 2,300 women with breast cancer who have also had estrogen receptor studies performed are available for analysis. A number of analyses were carried out during the year and several others have been planned. These include not only the prognostic significance of estrogen receptor values but also analysis of serum data and biological markers for breast cancer.

4) Analysis of the data on the psychological consequences of mastectomy is nearly completed. Greatest distress was found among those with Stage II (known positive) breast cancer compared with those with Stage I (node negative). Lowest level of distress was found among those with benign biopsy and among the healthy controls.

5) Two staff members serve as statisticians for the Lung Cancer Study Group, which consists of six major centers with a capacity to recruit over 150

Stage I lung cancer patients per year. Four prospective randomized trials are in progress but none has yet reached the analysis stage.

6) The staff has been collaborating with the Brain Tumor Study Group on analysis of data from a number of large-scale clinical trials.

7) A staff member is serving as statistician for a cooperative pilot study to develop procedures for a study of hospice care for terminal cancer patients. The study is aimed at assessing the psychological state of hospice patients and their immediate families, as well as the attitudes of hospice staff toward terminal care.

The above is only a partial list of the projects carried out by this group. In addition, this section has actively pursued a development of statistical methodology directly related to their work. This includes the following: estimation of the required duration of a clinical trial to assure a desired power for a given hazard ratio; methods for analyzing survival data in the presence of censoring mechanism; analysis of the properties of sequential tests applied to survival data; evaluation of serial marker measurements in patients at risk of recurrent cancer; development of an interactive computer program for analysis of patient survival adjusting for the effects of prognostic variables whose values change with time; development of a parametric survival model with time dependent covariates; experimentation with graphic display of survival curves which adjust for the effect of patient covariates; use of life table methods to smooth hazard and incidence data from clinical trials; experimentation with chi-square tests for equality of proportions; and analysis of the effect of multiple comparisons in two-way tables.

Mathematical Statistics

Dr. John Gart and his Mathematical Statistics and Applied Mathematics Section has provided statistical support and consultation both within the Division of Cancer Cause and Prevention and to other divisions at NCI. This has involved basic study design as well as data analysis. As an outgrowth of this activity, this section has developed basic statistical methodology which has applicability to the kinds of problems involved in their consultative work.

A brief summary of some of the activities of this section during the past year is as follows:

1) Work has been done on the design of the statistical analyses for an epidemiologic study of the relationship between dietary factors and cancer of the colon in Norway and in Minnesota. This involves assessing the effect of the various factors after adjusting for competing risk.

2) Ongoing statistical collaboration has been provided for a Biometry Branch study of non-melanoma skin cancer. During the year this involved an analysis of seasonal patterns of skin cancer incidence.

3) A variety of collaborative work has been carried out in the area of carcinogenesis research. This has involved the design and statistical

analysis of bacterial assays to study the mutagenic effect of mixtures of several known mutagens; an analysis of data on an experiment to investigate the apparent protective effect of early pregnancy on mammary tumor incidence; extensive statistical analyses of a large scale chronic toxicity study of environmental and industrial chemicals on rats; and a number of other projects involving the design and analysis of laboratory data.

4) The staff of the section collaborated with the Carcinogenesis Testing Program, now a part of the National Toxicology Program, on the analysis of various bioassays on carcinogenic experiments in rats.

5) A number of statistical analyses have been carried out in collaboration with investigators in the Division of Cancer Biology and Diagnosis. These include studies of precursors of cytotoxic lymphocytes, analysis of immune response data, evaluation of lung cancer immunotherapy trial, and a number of other studies.

6) A staff member has carried out several collaborative efforts with the Division of Cancer Treatment. These include: statistical methods for predicting pharmacological activity of potential anti-cancer drugs, design and analysis of in vitro mammalian cell assays for mutagenicity, and analysis of experiments on the use of intravenous alimentation to prevent cachexia in tumor bearing rats.

7) A variety of research has been carried out in the area of mathematical statistics, probability and applied mathematics. These include: a study of methods for combining estimators of relative risk from prospective stratified data; development of models for tumor growth and models for mammary tumor systems in rats; development of methods for identifying a cyclic trend; investigation of the properties of various estimators of relative risks for case control studies with multiple matched controls; and the development of methods for simplifying the derivation of score test statistics for a wide range of models.

Analytic Studies

Dr. Max Myers and his Biometric Research and Analytic Studies Section conduct research in cancer etiology, screening for early detection, prognosis, and in statistical methodology related to each of these areas. In carrying out these responsibilities the staff utilizes data from the cancer Surveillance, Epidemiology and End Results (SEER) Program and other available resources for analytic studies of factors that may be associated with the risk of developing cancer, for evaluating the effectiveness of screening programs, and for studies of factors associated with cancer patient survival. Some of the activities of this group over the past year include:

1) Continuation of work on the collaborative study with investigators from the Soviet Union on survival of breast cancer patients. Preliminary analyses indicate more frequent use of chemotherapy as an adjunct to surgery for the Soviet patients than for the U.S. patients. Further comparative analysis awaits the submission of approximately 2,000 USSR

cases. Data collection for the U.S. part of the study has been completed but at least three more years must elapse before it will be possible to compute 5-year survival rates.

2) Data were submitted to the NCI by the four registries that were former participants in the End Results Program to permit an assessment of trends in cancer patient survival from the early 1960's to the 1970's. These later data updated follow-up through 1978. Thus it has been possible to compare 5-year survival rates for patients diagnosed in 1970-73 with those for patients diagnosed in 1960-63. Among the ten leading sites of cancer there were significant increases in the 5-year relative survival rates over that decade for all but two -- stomach and pancreas. The most striking change over that time period was an increase in the 5-year survival rate for children under 15 years of age with acute lymphocytic leukemia -- an increase from 4% among those diagnosed in 1960-63 to 34% for those diagnosed in 1970-73.

3) Considerable work has been carried out in the area of cancer screening for early detection. A controlled clinical trial carried out by the Health Insurance Plan of Greater New York suggests the usefulness of annual screening for breast cancer using clinical examination plus mammography. After 12 years of follow-up the study group showed about 1/3 less mortality from breast cancer than the control group. A study of bladder cancer screening is being carried out collaboratively with other staff members in Field Studies & Statistics. This is an evaluation of the bladder cancer screening program at the Dupont Chambers Plant and includes all employees who ever participated in the urine cytology program at Dupont. Data are now being collected, records are being screened, and follow-up status is being determined. Work is continuing on the development of theory for the evaluation of screening programs using methodology from renewal theory. Topics being investigated include age dependence, parameter estimation, lead time, length biased sampling, and mortality measures. An age dependent mathematical model for screening is under development. The basic variables are age at entry into the pre-clinical state, pre-clinical state sojourn time, and age at screening for observation. These results lead to a more complete understanding of length bias in screening than has been possible previously.

4) Data from the End Results Group are being used to study the association of treatment with the risk of subsequent cancer for cancer patients diagnosed during 1935 to 1973. Three collaborative studies are being conducted with the Environmental Epidemiology Branch. These are: a study of second cancers following radiation for cervical cancer, the preliminary results of which show an excess of second cancers including leukemia, lung, bladder, kidney and genital cancers. The second is a case-control study to evaluate the risk of endometrial cancer following estrogen treatment for breast cancer, and the third is a collaborative study on the extent to which subsequent primaries occur following a diagnosis of Hodgkin's disease. As an outgrowth of the national bladder cancer--artificial sweetener study, a study of occupational exposures, particularly those in the automotive industry, in relation to possible elevated risk of developing bladder cancer, is being carried out in the

Detroit area. Two control groups are being used -- one, a group of hospital controls and the other, population controls. Data collection has been completed and detailed analysis is now being carried out.

5) A detailed analysis of the Third National Cancer Survey data (1969-71) has been carried out to study the association of cancer incidence with income and education. An important aspect of this study is an analysis of the effect of adjusting for differences in socioeconomic distribution on the risk of specific cancers among Blacks relative to those among Whites.

6) A series of methodological investigations related to analytical studies has been carried out. These include: the use of Monte Carlo methods to investigate the small sample adequacy of both the chi-square and an approximation to the exact conditional distribution of the Mantel-Haenszel statistic. The investigation showed the importance of considering adjustment for discreteness, whether or not to correct for continuity, number and size of the tables in analysis, and the nature of the underlying distribution as to whether symetric or not. A number of statistical methods are being studied for use in monitoring disease, for cluster analysis and for other kinds of epidemiologic studies. Relative survival rate methodology has been used to investigate the relationship between cancer patient survival and mortality attributed to the diagnosed cancer. The analysis thus far seems to indicate that there may be a number of deaths due to cancer which are not reported as such.

International Studies

During the past year research on stomach cancer and precursor lesions continued in Japan, Hawaii, and Colombia. Research also continued on colorectal cancers in these areas. The Norwegian migrant studies are continuing and a concerted effort is being made to analyze large data sets in Minnesota and Norway for the possible relationship to dietary factors and specific gastro-intestinal cancers. Preliminary analyses of data from the SEER Program indicate that the risk of nasopharyngeal cancer among the Chinese population in San Francisco, relative to that among Whites, is about 16 compared with a relative risk among the Hawaiian-Chinese of about 8. This is consistent with the preliminary inspection of the cancer mortality maps in the People's Republic of China, in terms of the areas of origin of these two U.S.-Chinese populations. Further analyses of these differences will be carried out during the coming year.

Skin Cancer

Stimulated by the need for data on the possible effect of increased ultraviolet radiation due to depletion of the ozone layer on the incidence of non-melanoma skin cancer, Joseph Scotto of the Biometry Branch has been carrying out a study of skin cancer incidence in 8 areas around the country. During this year, two new areas were added to provide more reliable national estimates of the morbidity from non-melanoma skin cancer, as well as epidemiologic data on host and environmental factors other than solar ultraviolet that may be associated with increased risk.

Psychological Factors in Relation to Cancer

Dr. Bernard Fox of the Biometry Branch staff has been participating in or monitoring a number of studies investigating the possible relationship between psychological factors and the occurrence of cancer. Prospective studies on four cohorts are being pursued -- 1) an employee cohort on the relationship of depression test scores to cancer mortality for the next 20 years; 2) a college cohort on the relation between scores in men on 15 psychological items and colon cancer mortality over the next 35 years; 3) follow-up of an adult Swedish county cohort for 20 years after an initial 10-year follow-up indicated a relationship of cancer mortality and specific psychological test scores; and 4) follow-up of a cohort to study the relationship between presence or absence of type A personality to cancer mortality over the next 20 years. Psychological test data are available from the initiation of each of these studies.

Computer Science

The Computer Science Section headed by Mr. Theodore Weiss provides computer support for a good deal of the research of the Biometry Branch through direct service as well as through the management of a large computer support contract. It is also heavily involved in the development of design and software for computer systems underlying the operation of large cancer registries. In addition, this section provides consultation on computer problems to other parts of the NCI. This section has coordinated the development of a prototype data management system for the SEER registries. During the year the core system was installed in the California Tumor Registry and it is currently being adapted for installation in the Connecticut Tumor Registry. Some aspects of this system are also being used for the Louisiana Tumor Registry and further modifications of it are being adapted for the Detroit Tumor Registry.

Plans for the Immediate Future

During the year the SEER Program was the subject of considerable discussion by the Board of Scientific Counselors of DCCP. In large part, this resulted from the report of the site visit to the Biometry Branch which focussed heavily on the SEER Program. Among the major issues was the cost of the program which now totals slightly over $10 million in contract funds. Following the report of the site visit, the Biometry Branch staff held a meeting with the SEER principal investigators to discuss ways in which the program could be streamlined and the cost correspondingly reduced. Among the major items being considered for modification are: reduction of the requirement for active follow-up in every SEER registry, reconsideration of the necessity of collecting data on detailed extent of disease and a re-examination of the computer costs across the SEER program. Analyses of these issues are now being carried out and decisions for changes will be made by the fall of 1980. Meanwhile, the Board of Scientific Counselors has appointed a sub-committee to "review the SEER Program." The Biometry Branch staff will explore with this sub-committee the possibility of specific major changes in or alternatives to the current SEER program. It is hoped that out of this will emerge a more

efficient way of achieving the basic objectives. Since the SEER Program has now collected five years of complete incidence data, a concerted effort is now being made to place these data in the public domain, both in the form of publications containing detailed data and in the form of public use tapes. A 1,000 page monograph presenting incidence and mortality data for the period 1973-77 will be published in 1980, and a series of smaller volumes, each pertaining to a specific site, will be published as NCI publications during 1980. Each will present current data on incidence, mortality and survival along with some comparisons with earlier data. In addition, the SEER data will serve as a basis for a number of papers on specific issues, to be submitted for publication in journals.

Some of the Biometry Branch staff effort will be devoted to collaboration on the Japan-Hawaii Cancer Study. Preliminary analyses on the cases of cancer of the colon, rectum and stomach that have been accumulated thus far have revealed that, for colon cancer in particular, serum cholesterol levels, as determined from initial examination, are unusually low. This has been corroborated by data from at least two other large prospective studies and will be the subject of more detailed analyses based on a larger number of cases during the coming year. In addition, the original 24-hour diet recall data are being recoded to take into account initial data obtained at the outset of the study which had never been processed. This will lead to a re-analysis of the relationship between dietary factors and the occurrence of colorectal cancer.

Several issues related to endometrial cancer will be explored during the coming year. Since the beginning of the SEER Program in 1973 it has been noted that the incidence rates for cancer of the uterine corpus have been higher in San Francisco, Seattle and Hawaii than in any of the other SEER areas. Further preliminary analysis reveals that this difference has occurred primarily in the age groups from 55 to 70, which suggest the possibility that greater use of post-menopausal estrogens on the West Coast may be a factor in these differences. Further analysis of this will be carried out. The unusually low rate of cancer of the uterine corpus in the New Orleans area suggest that there is a possibility of an artifact in the data. Investigations thus far, however, have not been able to identify such an artifact. Therefore, this will be further investigated. Meanwhile, one of the critical problems in understanding differences in endometrial rates across geographic areas is the extent to which prior hysterectomies have been done, thus reducing the number of women at risk of endometrial cancer. To the extent that this varies across geographic areas, this factor could have considerable influence on differences in the incidence rates unless the denominators are appropriately adjusted. Exploration of this problem and development of ways of estimating the actual population of women at risk will be carried out.

Plans are under way to bring in a Visiting Fellow from the People's Republic of China to spend a year on a collaborative study of cancer incidence in Shanghai compared with that in a large metropolitan area in the U.S. Since there are two populations (San Francisco and Hawaii) in which we already have ongoing data collection on substantial Chinese populations, these would be natural settings for such a comparative study. Hopefully, the analyses carried out during the coming year will lead to specific hypotheses which would then be the subject of further research during the years to come.

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REPORT
CLINICAL EPIDEMIOLOGY BRANCH
OCTOBER 1, 1979 THROUGH SEPTEMBER 30, 1980

"In the fields of observation, chance favors only the mind that is prepared."

Quoted by Rene Vallery-Radot in the Life of Pasteur (1927)

Clinical Epidemiology is a form of observational research in which one must make the most of natural occurrences to determine the causes and mechanisms of disease. Our approach is not traditional, but has proved to be continuously productive. Specifically, the Clinical Epidemiology Branch (CEB) seeks peculiarities in the occurrence of cancer in persons, families, communities or industries that may lead, in conjunction with recently developed laboratory research, to new knowledge of biology. In this way, study of human disorders may illuminate areas for which no animal models are yet known. Such observations may lead to new concepts of early detection and prevention.

Staff

Dawn D. Hassinger, Ph.D., M.D., after two years as a Clinical Investigator, returned to Yale University as an Oncology Fellow in August, 1980. The professional staff consists now of six physicians trained in pediatrics, internal medicine, oncology, hematology, human genetics and/or epidemiology; a biostatistician; a geneticist; two masters-level epidemiologists; and a computer technologist.

Clinical Activities

A main interest of the Branch has been to ascertain patients with unusual personal or family histories of cancer sometimes associated with diseases other than cancer. During the year, several of our observations have been greatly advanced by laboratory research done by others. We have continued, for example, to collect specimens of skin for fibroblasts from patients with the aniridia-Wilms' tumor syndrome, first described by us in 1964. All such cases show partial deletion of a short arm of chromosome 11. These observations, coupled with our report during the past year of a consistently found translocation from chromosome 3 to 8 in a Boston family with ten members affected by renal cell carcinoma, have added greatly to the understanding of susceptibility to cancer and to the role of mutations affecting germ cells in relation to others affecting somatic cells (i.e., Knudson's hypothesis).

Family studies: As time passes, additional cancers are occurring in families already under study, often predictably in members who were in the line of descent of affected relatives. Double primaries have also been prominent in these families. The reasons for this tremendous host susceptibility to cancers of dissimilar type have yet to be elucidated,

but through the use of techniques provided by the rapid advances in molecular biology and somatic cell genetics, a means for understanding them may soon be at hand. This applies not only to the role of genetics, but also to environmental interactions in the susceptible host.

In one such family, seven members of which have developed acute myelogenous leukemia through the maternal line, evidence of some defect in DNA repair has been found in affected members whose skin fibroblasts have been studied under our contract with Atomic Energy of Canada, Ltd. The results are in the same family members whose fibroblasts in culture displayed increased transformability by a simian virus 40 when studied by Dr. George J. Todaro in 1969. The purpose of the contract is to explore DNA repair defects as an explanation for certain family or individual susceptibilities to cancer, to the effects of ionizing radiation or the effects of chemotherapy. Human cells that are sensitive to environmental agents in culture may be useful to screen for human mutagens (carcinogens) in the future. In any event, the contract will help evaluate the reliability and value of DNA repair studies for more general application in clinical research. From August, 1978, until February 15, 1979, thirty strains collected by NCI plus twenty others have been studied under the contract. Three other families with leukemia do not show the DNA repair abnormality mentioned above. Fibroblasts from a family with Hodgkin's disease and radiogenic breast cancers displayed radiosensitivity under hypoxic conditions. With regard to tuberous sclerosis, two of three strains tested to date are sensitive to ionizing radiation. This is intriguing, because one of the three patients in the initial clinical report describing radiation sensitivity in ataxia-telangiectasia had features of tuberous sclerosis. Preliminary studies of four patients with Gardner's syndrome demonstrate sensitivity to the chemical, MNNG, in two. The contract will complete its 3-year non-renewable course in June, 1981.

In the absence of its own laboratory, the Branch would greatly benefit from a contract with a research laboratory competent in a variety of techniques for studying somatic cell genetics. A "sources sought" statement has been published to this end, and two responses are currently under review.

Etiologic ward rounds: New cases of potential etiologic interest come to our attention at ward rounds, in clinics, and by consultations requested at local hospitals -- also by mail or by telephone. The volume of consultations is substantial, and has led, for example, during the past year to identification of Dilantin as a transplacental carcinogen when we learned of a fourth case of neuroblastoma in the U.S. since 1976 in a child with the fetal hydantoin syndrome. Finding such new information, interpreting it and making it generally known is a main function of the Branch. The approach is ad hoc. It depends on seizing opportunities as they arise. Thus we cannot specify what diseases we will be studying in the future. We can only say it will be more of the same, and offer our list of publications as evidence of past productivity, and claim that an approach that has worked until now will continue to work. The approach is different from that followed by grant- or contract-supported research, for

it is highly unstructured and more concerned with generating than with testing hypotheses. We hope to set an example of a research style that differs from usual and will spread at least in a small way to universities and clinicians in general.

We have tried to enhance this spread by having our staff make etiologic rounds regularly at nearby universities (Georgetown, Children's Hospital National Medical Center, NCI, Johns Hopkins, the University of Maryland Hospital and the Sidney Farber Cancer Research Foundation), and intermittently by rounds and lectures on invitation by universities and other medical groups elsewhere in the U.S. The Branch bibliography contains evidence of observations gleaned from ward rounds; e.g., trilateral retinoblastoma in a child at D.C. Children's Hospital with both eyes and the pineal gland (the "third eye") affected by tumor due apparently to involvement of retinocytes that are naturally present in the pineal, but have not been recognized as a source of disease in that gland. Two other unreported cases were subsequently located in Philadelphia and in Amsterdam, the Netherlands, in addition to two others reported in the medical literature. The observation fills a gap in our clinical understanding, tells us something more about the pineal gland than we previously appreciated, and relates once again to Knudson's hypothesis which can predict the frequency with which the pineal will be involved in patients with the hereditary (multifocal) form of retinoblastoma.

Establishment of a Human Genetics Clinic at NIH: A major development during the past year, through the efforts of Drs. Lamon and Parry in conjunction with Dr. Joseph Schulman of NICHD, has been the establishment of a Human Genetics Clinic for all of the institutes at NIH. The clinic now appears to be a success, with more than 250 patients seen during its first year. The Clinic represents a coalition of talent for the study of cancer families (a substantial number of the total), and provides the facilities we require to examine patients of unusual interest and to obtain specimens for laboratory research. Often in the past we have written that progress in cancer etiology is fastest when an interaction occurs among epidemiology, clinical medicine and laboratory research. The Clinic helps us to practice what we preach.

Chromosome maps of cancer: A map has been prepared showing chromosomes known to have abnormalities in number or structure in leukemia, lymphoproliferative disorders or other solid tumors. Nine of the 23 chromosome-pairs are not yet known to have consistent cytogenetic abnormalities associated with specific cancers.

Neurofibromatosis: The Branch has long had a smouldering interest in neurofibromatosis, an autosomal dominant hereditary disorder with multiple tumors both superficial and internal, and much too often malignant. This interest was heightened by two studies published by the Branch a year or so ago which indicated that non-neural tumors, specifically non-lymphocytic leukemia and rhabdomyosarcoma, occurred excessively in people with the genetic disorder. Neurofibromatosis (NF) affects about 100,000 people in the U.S. Several other investigators elsewhere developed an interest in studying the disease at about the same time we did. New laboratory approaches

to carcinogenesis in relation to the genetic defect responsible for NF may be appropriate. To define the possibilities, the Branch held a national meeting in June, 1979, at which biologic approaches (epidemiologic, clinical and laboratory) were defined, along with prospects for the future. The proceedings will be published by the two organizers of the meeting, Dr. John J. Mulvihill of our Branch and Dr. Vincent M. Riccardi of the Baylor College of Medicine, Texas Medical Center.

Since then, the theatrical production, The Elephant Man, drew public attention to the disease, especially through publicity in the news media when the play opened in the Washington area. We received almost 100 telephone calls from people in the community many of whom have real but unmet problems with regard to the disease. ("My wife died recently of NF at the age of 43. My 9-year-old son, at present unaffected, has seven large café-au-lait spots. What should I do?") A summary of this experience and its medical and research implications is being prepared. A comprehensive investigation of NF families is being made in the newly established Genetics Clinic in collaboration with clinicians and laboratories in other Institutes or outside NIH.

Radiation Effects

Dr. Gilbert W. Beebe, an Expert Consultant in the Branch, devotes much of his time to the re-emergence of fear about low-dose radiation effects. As a sociologist-statistician with an extended experience at the Atomic Bomb Casualty Commission in Japan, he meets regularly as an advisor at the NIH level with Dr. Fredrickson and at the NCI level with the NCI Interim Project Team on the Biologic Effects of Low Level Ionizing Radiation. He also contributed substantially to Report III of the NAS's Committee on the Biological Effects of Ionizing Radiation. He was honored in December, 1979, by the Harvard School of Public Health, when he gave the annual Cutter Lecture there.

Dr. Beebe has also been extremely helpful both within the Institute and beyond in matters of national importance with regard to epidemiologic research, such as advising on new privacy laws which otherwise could be extremely limiting to such research.

Chemicals

A substantial amount of time during the past year has been claimed by activities concerning chemical contaminations, food additives (the Food Safety Committee of the NAS-IOM), multi-chemical exposures at the Love Canal in Niagara Falls (New York State Health Department) and dioxin in Seveso (NAS-Italian Institute of Public Health). A means for dealing with these and future chemical contaminations requires integration of knowledge concerning epidemiological, clinical and laboratory studies. A strategy for responding to such situations is being developed by the NAS-Italian group on the basis of a 3-day symposium held at the National Academy of Sciences, March 17-19, 1980. Dr. Miller was co-chairman of the meeting and will edit the proceedings.

Three-dimensional Maps

Through the use of programs developed for the computer by Mr. F. W. McKay and Ms. M. Hanson of our Branch, a series of three dimensional graphs have been produced which help to visualize the changes over time from 1950 until 1977 in type-specific cancers by age, and sex for whites and for non-whites. In the aggregate, the graphs provide a panoramic view of trends in cancer mortality which sometimes reflect cause (cigarette-smoking), the effects of therapy (childhood leukemia), or a steady marked decline for unknown reasons (stomach cancer). A volume will soon be submitted for publication of the graphs and the accompanying tables.

Foreign Affairs

In January, 1980, after a year as Director of the Office of International Affairs for NCI, Dr. Miller elected to give up that responsibility to devote full time to cancer etiology. International activities with Japan and China in particular continue to be a strong interest of the Branch. Drs. Miller and Beebe of CEB and Drs. Blot and Land of the Environmental Epidemiology Branch are working to enlarge the U.S. presence at the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki with respect to epidemiology and statistics. The contribution by the few Americans present at RERF has been enriched by the 2-year appointment there of Dr. William J. Schull, who has had long experience in Japan and in the United States in the scientific design of population studies. The change in the status of the organization in 1975, when the Atomic Bomb Casualty Commission became the RERF under Japanese management, was accompanied by a diminished influence of the Americans there. To improve prospects for the future, re-enforcements were needed. Several top-notch scientists agreed to join Dr. Schull in Hiroshima during the remainder of his assignment there, in an effort to preserve and increase the scientific value of this most important resource for information on the human effects of radiation exposure.

In September, 1977, Dr. Miller visited the People's Republic of China, when he was a member of a U.S. Cancer Delegation under the auspices of the Committee for Scholarly Communications (CSCPRC) with the People's Republic of China (NAS-NRC). To extend important observations concerning peculiarities in the occurrence of cancer in China as reported by the Delegation, Dr. F. P. Li and his wife Dr. E. L. Shiang, were awarded Senior Scholarships by the CSCPRC to study there for three months beginning in mid-August, 1979. Most of their time was spent in Beijing, but they visited Shanghai, Canton, Nanking and Tianjin. The interval of study proved to be extremely well timed, for it came just after Secretary Califano signed the U.S.-China Health Agreement, and Drs. Li and Shiang were able to prepare NCI and the Chinese for the NCI Delegation's visit, November 16-22, 1979. In consequence, NCI got an early start in its binational activities with the Chinese, which feature epidemiology because the Chinese have a natural talent for observational research. Drs. Li and Shiang were able to help in the preparation of the English text for the atlas soon to be issued concerning cancer mortality by county for the entire PRC.

Dr. Li Ping, Vice Director of the Cancer Institute (Beijing) of the Chinese Academy of Medical Sciences was awarded a Lectureship for six weeks in the United States beginning on March 23, 1980. The Clinical Epidemiology Branch served as her primary host in this country. She was accompanied by Dr. Zhang Yu-hui, Deputy Chief of the Department of Immunology at her Institute, who served in part as an interpreter as well as an independent scientist. The visitors spent three days in Boston with Drs. F.P. Li and E.L. Shiang, two days in Hershey, Pennsylvania, with Dr. Miller at the annual meeting of the American Epidemiological Society, where Dr. Li Ping spoke about cancer epidemiology in China, and three weeks at NCI where Drs. Li and Zhang had a series of small group discussion with members of the three Branches in Field Studies and Statistics. Dr. Li's primary interest is in maps of cancer mortality in China for which she provided the leadership over the past five years. In consequence, she and her 600,000 collaborators have produced a remarkable volume which shows marked clustering of an epidemic nature for half a dozen cancers in China. Dr. Li sought advice on comparing the study done in China with that done by NCI of cancer mortality by county, each of the studies having been made independent of the other. Now she would like to have the data from both standardized in the same way, and to learn more about the users of computers in preparing maps.

Veterinary Studies

In 1964 the Branch established the Veterinary Medical Data Program (VMDP) for systematically collecting, storing and retrieving data on domestic animals seen at 14 veterinary medical colleges in the United States and Canada. More than 1.7 million discharge diagnoses have been collected, among other information. Included are 40,000 tumors. When a plateau in the use of information seemed to have been reached in 1977, the collection of data was transferred to Associated Veterinary Medical Data Participants, Inc., Urbana, Illinois to be available for public use. A report and a variety of tabulations concerning the tumors in the series has gone to press for publication by the Branch as an NCI Monograph.

Other Activities

The Childhood Cancer Etiology Newsletter issued monthly by the Branch is now in its sixth year. The Newsletter goes to almost 800 persons interested in childhood cancer throughout the world, and has been a source of new ideas and fresh interest in pediatric cancer etiology both for us and for the recipients.

A great deal of time has been given during the year to synthesizing information, for review and new insights. The need in the coming year is to devote more time to reporting original research.

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REPORT
ENVIRONMENTAL EPIDEMIOLOGY BRANCH
NATIONAL CANCER INSTITUTE
October 1, 1979 through September 30, 1980

This is the fifth report of the Environmental Epidemiology Branch which was created in December 1975. The objective of the Branch is to generate and test ideas concerning the environmental and host determinants of cancer by a broad range of epidemiologic studies based on knowledge and application of clinical medicine and oncology, statistical methodology, new developments in carcinogenesis, and resources best available at the national level. The allocation in FY 1977 of several new positions has permitted an expansion of the research program, enabling the Branch to serve more effectively as a focus within the Institute for epidemiologic initiatives. Joining the Branch this year were Dr. Regina G. Ziegler, who has a Ph.D. in biochemistry, an M.P.H. degree, and experience in nutritional studies; Dr. Robert J. Biggar, a pediatrician with experience in infectious diseases, who transferred from the Laboratory of Viral Carcinogenesis and the Burkitt's Tumor Project in Ghana; and Dr. Robert Spirtas, who has a Dr. P.H. in biostatistics and background in occupational epidemiology at the National Institute of Occupational Safety and Health. Dr. Eva Buiatti, a physician specializing in occupational epidemiology at the Centro per le Malattie Sociali in Florence, became a visiting scientist. Appointed as Staff Fellows were Dr. Arlene F. Kantor, a Ph.D. in epidemiology from Columbia University, and Dr. Lynn R. Goldin, a Ph.D. in genetics from the University of North Carolina. Also joining the Branch were Diane J. Mundt (Sc.M., Harvard University) and Ruth A. Kleinerman (M.P.H., Boston University) in the Radiation Studies Section, Barry A. Miller (M.S.P.H., University of North Carolina) in the Occupational Studies Section, and Michelle Morin (M.S., University of Massachusetts) in the Population Studies Section.

RESEARCH PROGRAM

Geographic Studies

Demographic patterns--To provide a systematic means for identifying geographic variation and clustering, the Branch has analyzed U.S. cancer mortality on a county level and prepared computer-generated color maps for 35 cancer sites. First, an atlas of cancer mortality was published for the white population, followed by a companion atlas for the non-white population covering the years 1950-69. At present maps are being prepared on cancer mortality for the time period 1970-75. Maps for non-neoplastic diseases have also been prepared, emphasizing conditions that predispose to cancer or share etiologic factors. The clues derived from the cancer maps have been pursued actively by the Branch, using a stepwise approach of correlation and analytic studies summarized this year in review articles (1,2).

To seek explanations for the geographic variation in cancer across the U.S., correlation studies have related the county mortality rates with demographic and environmental data available at the county level.

The starting point may be a particular environmental exposure. In areas with large shipyards during World War II the mortality rates for respiratory cancers were found to be consistently elevated (3,4). In counties with metal electroplating and coating industries, there were elevated rates for several cancers, especially of the esophagus and larynx (5). In other correlation studies, the starting point is a particular cancer site. Mapping of renal cancer revealed a clustering of elevated rates in the upper north central part of the country, and correlations were seen with the percentages of residents of German, Scandinavian, and Russian descent (6). Leukemia mortality was high among people over age 55 in the north central and south central states (7). The regional excesses involved primarily acute myeloid leukemia, and correlations were found with certain food industries and other occupational and agricultural indicators. Mortality from non-Hodgkin's lymphoma was elevated also in the central part of the country and along coastal counties of California, and revealed positive correlations with socioeconomic status (8). The rates for this tumor have risen over time, particularly for histiocytic lymphoma. Especially pronounced has been the upward trend in rates for multiple myeloma, especially among blacks in all parts of the country (9). A mortality study of mycosis fungoides revealed a predominance among males, blacks, and urban residents, particularly in the northeastern U.S., and geographic correlations with various industrial exposures (10). The changing time trends for breast cancer mortality were evaluated by age group, and seemed related to the fluctuating patterns of childbearing during this century (11). A survey of thyroid cancer in Connecticut showed increases in the papillary and follicular cell types, consistent with the effects of radiation therapy, given previously to children with benign conditions of the head and neck (12). Attention was paid to U.S. population groups traditionally thought to have a deficiency of cancer overall, and on the high-rate cancers that nevertheless are seen in such "low-risk" groups (13). Also reported was the increased risk among Alaskan natives of cancers arising from the nasopharynx, salivary gland, kidney, gallbladder, liver, and connective tissue (14).

Field studies--The final step in geographic studies is the testing of specific hypotheses by case-control investigations in high-risk sections of the country (15-17). A major effort is underway to evaluate risk factors for lung cancer, particularly in southern coastal areas where the rates are highest in the U.S. (18). An earlier Branch investigation in coastal Georgia found a significantly increased risk associated with employment in area shipyards that operated only during World War II. This year an interview study was completed in Tidewater Virginia, where respiratory cancer rates were as high as in Georgia and where shipbuilding was the major employer during the war and continues to be so today (19). There was a 70% excess risk of lung cancer, adjusted for cigarette smoking, associated with shipyard employment initated before 1950. No increase was found for those who began work in 1950 or later, and no appreciable difference was noted between career and temporary employees who began work before 1950, highlighting the importance of wartime exposures. A synergistic interaction between shipyard exposures and smoking was consistent with previous observations on asbestos workers. Mesotheliomas were also

excessive in the Tidewater area (20). Interviews were completed with the next-of-kin of 56 of the 61 white males diagnosed with mesothelioma during the years 1972-78. Three-fourths of the cases had been employed in area shipyards, mostly starting before 1950. Many worked as pipecoverers where asbestos exposure was likely to have been heavy. Although the incidence of mesothelioma was not high among females in the Tidewater area, four of the five women with this tumor were the wives of shipyard employees.

Lung cancer, among other neoplasms, was the focus of a death certificate survey in high-risk areas of southern Louisiana, in collaboration with Tulane University. Among patients dying with lung cancer, there was a two-fold excess risk associated with shipbuilding and fishing (21). Some association was seen with the petroleum industry and with Acadian ancestry. Death certificate differences between bladder cancer cases and controls were not as pronounced, but a link between pancreas cancer and petroleum industry jobs offered some clues for further study (22). To obtain more detailed information on characteristics of cancer patients in Louisiana, the Branch is collaborating with the EPA and Louisiana State University in case-control interview studies of lung, pancreas and stomach cancers. A case-control interview study of respiratory cancer along coastal Texas was also begun with the University of Texas School of Public Health. Nearly completed is a similar study in northeast Florida in conjunction with the University of Miami. Also near completion is a case-control interview investigation of lung cancer in a tri-county area of eastern Pennsylvania, where a large nonferrous metal smelter is located. The interview data will be linked with environmental measurements previously collected by other agencies in the area.

A large-scale interview study of bladder cancer in several parts of the country (described below) includes several high-risk areas of the country. A separate investigation of bladder cancer is underway in northern New England, where the rates are elevated in both sexes. To clarify the relationship between woodworking and nasal cancer, an interview study of patients is underway in Virginia and North Carolina. Also, in North Carolina a case-control study of oral cancer has been conducted with the University of North Carolina to identify factors responsible for the high rates for this cancer among rural southern women. Preliminary results suggest that snuff use is the major risk factor. To understand reasons for the clustering of renal cancer in the north central area, the Branch has undertaken a case-control study with the University of Minnesota.

Occupational Studies

Occupational studies have long played an important role in identifying environmental carcinogens. There are implications beyond the work force, since many agents spread from the work place to the surrounding environment. Although the extent of the hazards resulting from environmental pollution or contaminated consumer products is not clear, there is no question that occupational groups are invaluable as sentinels for identifying and evaluating risks to the general population. Occupational studies are

initiated by the Branch for various purposes: (a) to explain "hot spots" uncovered by county-by-county surveys of cancer mortality; (b) to identify high-risk subgroups within broad industrial categories; (c) to pursue clues provided by animal bioassays or alert clinicians; (d) to estimate risks associated with known carcinogens in user rather than producer industries; (e) to assist outside agencies or institutions in evaluating the health experience of their workers; and (f) to provide insights into the basic mechanisms of carcinogenesis. A variety of approaches are taken, especially retrospective cohort and proportionate mortality studies, utilizing data resources from industrial firms, labor unions, professional associations, state vital records departments, the Social Security Administration, and other government agencies. Covered elsewhere in this report are the case-control and correlation studies which may help identify occupational hazards.

Several studies were reported this past year. Preliminary results from a survey of non-agricultural pesticide applicators revealed an excess of deaths from lung cancer, particularly among workers licensed for ten or more years (23). A proportionate mortality study of Government Printing Office employees revealed excesses of multiple myeloma among composing room workers in contact with lead compounds, and leukemia among bindery workers possibly exposed to benzene (24). A proportionate mortality study of workers in the metal polishing and plating industry showed excesses of esophageal and liver cancers, possibly due to exposures to metal fumes, solvents, and strong acid or alkaline substances (25). A study of causes of death among veterinarians revealed significant increases of leukemia and Hodgkin's disease, and cancers of the brain, liver, and skin (26). The mortality from cancer was greatest among veterinarians in clinical practice, raising the possibility that specific work exposures (e.g., medical x-rays, animal viruses) may be carcinogenic. Analysis of occupations recorded on death certificates from Nebraska (1957-74) revealed an increased risk of leukemia among farmers, especially from heavy corn-producing counties (27).

Several large-scale mortality surveys of industrial groups were also carried out. A study of active and retired employees of a pharmaceutical company indicated excesses of respiratory cancer and leukemia among female production workers, melanoma among male production workers, and respiratory cancer among male maintenance workers (28). These associations could not be traced to specific chemical exposures, but provide leads to further studies. An evaluation of mortality among members of the Oil, Chemical, and Atomic Workers International Union (OCAW) indicated elevated frequencies of cancers of the stomach, kidney, brain, leukemia, and multiple myeloma among petroleum refinery and petrochemical workers who were OCAW members for at least ten years (29). Mortality ratios for cancers of the stomach, brain, and lung were especially high in specific plants, where more definitive studies are planned. A proportionate analysis of 202 deaths among aircraft spray painters exposed to zinc chromate paints revealed an excess of lung cancer, consistent with the risks seen in chromium manufacturing processes (30). A survey of iron foundry workers exposed to polycyclic hydrocarbons revealed excess mortality from cancers of the respiratory and digestive systems (31).

A methodologic comparison of the proportionate mortality ratios (PMRs) and standardized mortality ratios (SMRs) indicated that PMRs will overstate or understate disease risks depending on whether the overall mortality of the study group is lower or higher than the comparison group (32). Using a conversion rule, an equation was developed to estimate SMRs from cause-specific PMRs, thereby allowing more precise estimation of underlying disease risks when the population-at-risk is unknown. A descriptive study of smoking, an important confounder of occupational studies, evaluated the characteristics of smokers, exsmokers, and nonsmokers in a working population (33). Despite numerous comparisons of physical, occupational, and social characteristics, few differences were seen among groups. This provides little support for the constitutional hypothesis of smoking risk.

A comprehensive review of occupational cancer was prepared this year (34). Although results are not yet available, studies are underway to evaluate the effects of various industrial exposures. A cohort study of copper smelter workers will update an earlier Branch study that linked lung cancer with exposures to arsenic trioxide. Cohort studies of stainless steel welders and jewelry manufacturers should help assess the risk of cancer after exposure to metals and organic solvents that have shown carcinogenic activity in laboratory animals. A cohort study of retired fur workers will clarify the hazards of dyes that are carcinogenic in laboratory animals and used extensively as hair dyes. A study of the mortality patterns of workers in a large leather tannery and shoe manufacturing plant also focuses on potential exposures to dyes, solvents, leather dusts, and possibly asbestos in view of occurrences of mesothelioma in shoeworkers (35). Mortality studies are also underway for the following occupational groups: chemical plant workers exposed to benzene; taconite miners exposed to asbestos and fibrous dusts; embalmers exposed to formaldehyde and other chemicals; chemists belonging to the American Chemical Society; makers of tobacco involving contact with pesticide residues; and laboratory personnel previously employed at Fort Detrick, Maryland, to determine any effect of hyperimmunization through repeated vaccinations. Mortality studies of USDA employees, aerial applicators, licensed pesticide applicators, and persons poisoned by pesticides should help clarify the risks associated with pesticide exposure. Studies of artists, photographers and potters were initiated because of their contact with potentially hazardous substances including arsenic, lead, chromium, benzene and other solvents, and asbestos and fibrous dusts.

A number of collaborative studies with other government agencies or outside groups are underway. With the National Heart, Lung, and Blood Institute, an analysis of cancer mortality among 300,000 U.S. veterans by occupational categories and smoking habits should provide new leads to occupational hazards. Efforts are being made to extend the followup of this cohort from 1970 to the present to examine occupational factors in rare tumors. In collaboration with the Medical Follow-up Agency (NAS), a cohort study will evaluate the possible carcinogenic effects of exposure to tetrachloroethane, which was used to impregnate clothing against mustard gas during World War II. Studies of two worker groups (marine

inspectors and shipyard workers) with exposures to benzene, welding fumes, and asbestos have been initiated with the U.S. Coast Guard. A mortality study of chemical workers having contact with formaldehyde and formaldehyde-resins is being developed with cooperation from the Formaldehyde Institute following reports that this agent is carcinogenic in laboratory animals.

Radiation Studies

As pressure mounts to identify the health effects of low-level exposures to ionizing radiation, large scale studies of irradiated populations have been initiated. These include studies of over 100,000 cervical cancer patients treated with radium implants; 20,000 former tuberculosis patients who received multiple fluoroscopies; 3500 children exposed to head and neck irradiation during childhood; and 80,000 survivors of the atomic bombings in Hiroshima and Nagasaki. Radiation studies of latent period, dose response, interactions with host factors (e.g., age), and other risk factors have basic implications for theories of carcinogenesis.

To characterize the risk of radiogenic breast cancer, the three major sets of human data were analyzed in similar fashion. The exposed populations included tuberculosis patients who had multiple fluoroscopic examinations of the chest, mastitis patients given radiotherapy, and A-bomb survivors (36,37). The findings suggest the following: the risk of breast cancer is greatest in persons exposed as adolescents, although exposure at all ages carries some risk; the dose-effect relationship is consistent with linearity; fractionation does not appear to diminish risk nor does time since exposure, even after 45 years of observation; the interval between exposure and clinical appearance of radiogenic breast cancer is mediated by age-related factors (hormonal?) but is unrelated to dose. By pooling the available data from western women, estimates of radiogenic breast cancer risks were made: 10.4 excess cases/10^6WY-rad and 6.6 excess cases/10^6WY-rad for women 10-19 and 20+ years of age at exposure, respectively. Only limited data exist on the risks of radiogenic breast cancer in older women; in fact, a peculiar decrease in risk with increased dose was observed for A-bomb survivors aged 40-49 at exposure. This issue will be clarified by a collaborative study with Harvard University to evaluate the risk of breast cancer in tuberculosis patients who received multiple chest fluoroscopies after age 30.

The followup of women exposed to multiple fluoroscopic chest examinations in conjunction with pneumothorax treatment of tuberculosis continued (38,39). The findings reaffirm that repeated relatively low radiation doses pose some future risk of breast cancer, that the risk may be cumulative, and that a woman's lifetime risk of breast cancer may be determined in large part during her reproductive years. Exposures around menarche and during first pregnancy appear especially hazardous, so that proliferating breast tissue may be particularly sensitive to the carcinogenic effects of radiation. The estimation of breast, lung, stomach, pancreas and bone marrow doses from fluoroscopy has been refined and a mortality analysis performed (40). No excess of total cancer deaths, leukemia, lung cancer

or lymphoma was seen among fluoroscopically examined women. The mortality analysis is meaningful to the extent that upper levels of radiation risk might be excluded: 7.5 deaths/10^6WY-rad for leukemia, 1.5 deaths/10^6WY-rad for lung cancer, and 2.6 deaths/10^6WY-rad for lymphoma. Expansion of this study is underway in Massachusetts and Connecticut to evaluate further the risk of radiogenic leukemia and lung cancer in both men and women.

A 10-year international radiation study of 30,000 cervical cancer patients, treated in 9 countries and followed clinically with blood studies, failed to observe an excess of leukemia, although the mean bone marrow doses were large and a substantial excess was predicted (41,42). The absence of an effect suggests that a) high doses to small volumes of bone marrow may cause substantial cell-killing and minimal cell transformation; b) patients may not have been followed long enough to observe an effect since A-bomb studies indicate a longer latent period for older persons; and/or c) women may be less sensitive than men to radiogenic leukemia. A deficit of chronic lymphocytic leukemia was observed suggesting that radiation may actually protect against the development of this disease. A significant deficit of multiple myeloma was also found. Doses to body sites outside the pelvic area from radium are low (1-100 rad) and can be accurately determined. A feasibility effort is underway to enlarge and extend this study another ten years to evaluate organ-specific risks following low-level exposure.

Using resources of the Radiation Effects Research Foundation (Japan), studies were conducted that add new cancers (lymphomas and cancers of the esophagus, stomach and urinary tract) to the list of those known to be caused by radiation from the 1945 A-bomb explosions (43). Solid tumors as a group now outweigh leukemia as a radiation effect, in terms of absolute risk. The minimal latent period of most cancers was under 15 years and depended on age and site of cancer. Since effects appear generally stronger in Hiroshima than Nagasaki, it would seem that neutrons are more potent carcinogens than gamma rays (44,45). Cancer is clearly the major late effect of A-bomb radiation, and a non-specific aging effect is not supported by the data. Studies of breast cancer revealed a dose-effect relationship that was approximately linear at low doses with an effect at doses below 50 rad. The breast cancer incidence data provide an exception to the general rule of greater effect for neutrons than for gamma rays as the estimated risks per rad were practically identical for both cities. The intervals between exposure and the clinical appearance of radiogenic cancers of the breast and lung were unaffected by dose, whereas leukemia tended to occur earlier in the more heavily exposed groups. The mechanism for leukemogenesis may be fundamentally different from carcinogenesis generally, since age-related events appear to be required before radiogenic tumors of the breast and lung are induced. To evaluate the possible interaction between radiation and host factors that increase breast cancer risks (e.g., family history), a case-control study has been initiated in Japan. Expanded collaborative efforts with RERF are planned which include more direct involvement of Branch staff.

A study to evaluate the risk of head and neck malignancies among children irradiated for enlarged tonsils is continuing. This study includes surgical controls, and physical examinations are planned for both groups to evaluate the efficacy of "callback" programs and the significance of occult tumors found at screenings. Also continuing are a geographic correlation study linking uranium mill tailing deposits with cancer mortality in western counties; a cancer incidence study of over 36,000 patients treated with radioactive iodine for hyperthyroidism (with the FDA Bureau of Radiological Health); and analysis of sputum cytology data in uranium miners (46). The risk of osteosarcoma and fibrosarcoma of bone has increased among patients with Ewing's sarcoma treated with radiation (47), and surveys of radiogenic neoplasms are being conducted in patients with childhood cancer, breast cancer, Hodgkin's disease, and thyroid cancer. A collaborative study of 10,000 children irradiated for ringworm of the scalp in Israel was begun. A preliminary mortality and incidence study of X-ray technicians has been initiated, as well as feasibility studies of radiation-induced chromosome damage following multiple chest fluoroscopies and radiotherapy for cervical cancer. An evaluation was made of a well-publicized investigation of cancer among nuclear energy workers (48). Several review papers concerning the health effects following exposure to ionizing radiation were written, including a general overview of radiogenic cancer (49), a survey of cancers following medical irradiation (50), the effects of radiation on the immune system (51), the statistical aspects of estimating cancer risks from low doses of radiation (52,54), the epidemiologic issues surrounding low-dose studies (55), and the long-term effects of radiation upon the human fetus (56).

Members of the Branch also helped prepare several committee reports to assess the risks of mammography for breast cancer (National Council of Radiation Protection and Measurements), to review and reanalyze a mortality survey of cancer among atomic energy workers (Department of Energy), to evaluate the biological effects of ionizing radiation (National Academy of Sciences, and DHEW), to review the effects of low-level doses (NCI), and to evaluate the possible hazards resulting from the Three Mile Island nuclear power plant accident (NIH) (52,57-61).

Medicinal Agents

Drugs have been generally thought to contribute only slightly to the overall risk of cancer, but recent reviews by Branch members suggest that the hazard may be much greater than anticipated (62-66). This year several projects were undertaken to evaluate the carcinogenic effects of estrogen compounds. A case-control study of breast cancer using the Breast Cancer Detection Demonstration Project revealed increases in relative risk, primarily in women with a surgical menopause (67). Estrogens appeared to obliterate the protective effect normally associated with oophorectomy, and produced an increased risk with extended use. Nearly a four-fold excess risk was seen for cancers detected after the initial screening among users of ten or more years. The highest risks were seen when hormones were used in the presence of known risk factors including

nulliparity, family history of breast cancer, and benign breast disease. Another study involved 345 women with breast cancer and 611 controls, all members of a prepaid health plan (68,69). There was a significant excess risk among women who ever used conjugated estrogens; a dose-response relationship was seen with three different measures of dose, rising to two-fold following long-term use.

Another problem under study is the risk of developing cancer among patients treated with cytotoxic agents or immunosuppressive drugs. A system for monitoring the risk of second primary neoplasms has been implemented, in collaboration with the NCI Division of Cancer Treatment, utilizing the protocols of several cooperative trial groups. In one study no excess of leukemia or other tumors was found following low-dose thio-TEPA or FUDR adjuvant chemotherapy for large bowel cancer (70). Nearing completion is a large-scale survey to clarify the risk of leukemia among patients with ovarian cancer treated with alkylating agents. In a survey of 54 patients treated with cyclophosphamide for rheumatoid disease, 2 cases of bladder cancer were observed, about 100 times the expected number (71). In addition to the continued study of renal transplant recipients (see below), surveys are underway in collaboration with the Cleveland Clinic and the NIH Clinical Center to determine whether immunosuppressive and cytotoxic drugs increase the risk of cancer in patients with various autoimmune diseases.

Several compounds that are carcinogenic in laboratory animals were evaluated this year. A mortality survey of 338 women treated with isoniazid for pulmonary tuberculosis revealed no unusual cancer experience, but did uncover excess deaths from liver cirrhosis, suggesting that chronic as well as acute liver disease may complicate this treatment (72). A study of leprosy patients treated with dapsone is continuing.

Nutritional Studies

This year the Branch expanded its research to clarify dietary factors in cancer etiology. Several of the case-control studies in high-risk areas have probed for nutritional exposures. In two rural counties in Nebraska with a cluster of colon cancer, the risk was primarily among people of Czech ancestry and was associated with a high intake of fat and dairy products. In a case-control study of esophageal cancer among blacks in Washington, D.C., alcohol consumption was the primary risk factor and provided approximately 40% of the daily caloric requirement. After controlling for alcohol intake, the consumption of fruit and vegetables containing vitamins A and C was inversely related to the risk of esophageal cancer. The role of micronutrient deficiency is also being evaluated in case-control studies of lung cancer, and the influence of fat intake is being explored in breast cancer.

A case-control study using death records has been designed to evaluate the low rates of colorectal and breast cancer in the southern United States, including retirement areas with a large percentage of migrants

from the North (73). It is suspected that dietary changes following migration may exert a protective effect against the development of these neoplasms.

With HANES I, the first Health and Nutrition Examination Survey of the United States, 1971-75, the National Center for Health Statistics assessed the nutritional status of 13,000 representative American adults. The Branch is searching for geographic correlations between dietary and biochemical data from this study and the county rates for various cancers. The data are also being utilized for methodological studies of nutritional epidemiology. In cooperation with other Institutes and the National Center for Health Statistics, the Branch is preparing to followup all the adults examined in HANES I, in an effort to relate dietary habits with the subsequent risk of cancer.

With the Medical Follow-up Agency, a mortality survey of U.S. Army servicemen hospitalized for chronic alcoholism in 1944-45 revealed an excess for several causes of death, including cancers of the buccal cavity, pharynx, larynx, and esophagus (74). The findings support previous studies suggesting that alcohol potentiates the carcinogenic effect of tobacco smoke, perhaps through nutritional deficiencies or co-carcinogens that may be present in alcoholic beverages. Further investigations were suggested to clarify the remaining issues (75).

Case-Control Studies

Several case-control investigations were conducted this year, apart from the field studies in high-risk communities and studies of drug-induced cancer (described above). Interviews were completed from a large collaborative population-based study of bladder cancer (with the Food and Drug Administration) combining information from the New Jersey State Department of Health and ten areas of the SEER Program of NCI. This study involves 4000 bladder cancer patients and 7000 controls drawn from a probability sample of the general population. Data were collected on saccharin use, smoking habits, occupational history, sources of drinking water, hair dyes, coffee drinking, and medical history. The preliminary findings suggested no overall association with artificial sweeteners, but excess risks related to dose were seen among persons who smoked heavily or who had an otherwise low baseline risk (i.e., female non-smokers unexposed to occupational hazards). The findings suggest that artificial sweeteners may be weakly carcinogenic or co-carcinogenic, but the maximum likely magnitude of any such risk is small by epidemiologic standards (76-78). The bladder cancer study is being continued in greater Atlanta to better evaluate the effects of occupational exposure associated with textiles and dyes, and in greater New Orleans to clarify the role of pollutants in drinking water. A separate case-control study of bladder cancer involves patients under 21 years of age, their siblings, and a comparison group of other childhood cancers. The subjects and their mothers will be interviewed for prenatal and early life exposures to artificial sweeteners and other possible risk factors.

Nearly completed is a study of non-Hodgkin's lymphoma involving 91 cases treated at the NIH Clinical Center plus 121 sibling controls. The questionnaire probes lifetime occupational and residential histories, drug use, exposure to lymphoma cases, and detailed medical and family histories. A study has begun on 325 patients with testicular cancer treated at the NIH Clinical Center, Walter Reed Army Hospital, and Bethesda Naval Medical Center along with 325 controls, and mothers whenever possible, to obtain detailed information on prenatal and postnatal exposures to medicinal, occupational, and other environmental factors suspected in the origins of this tumor.

Another interview study involves 350 patients with ovarian cancer in the Washington, D.C., area and an equal number of women hospitalized for other conditions, to help clarify the influence of reproductive factors, exogenous hormones, contraceptive methods, and other possible risk factors. Also nearing completion is an interview study of 400 patients with intraocular melanoma, and an equal number of controls, in collaboration with the Wills Eye Institute in Philadelphia. Mail questionnaires are being sent to 180 patients with multiple myeloma participating in the Acute Leukemia Group B, plus their siblings, to elicit information on environmental and host factors. A similar study is being conducted on 270 patients with mycosis fungoides.

Case-control studies were also carried out on childhood neoplasms. Using data from the Connecticut Tumor Registry, a survey of Wilms' tumor revealed a four-fold excess in risk associated with lead-related occupations in the father (79). In collaboration with British investigators and the Oxford survey of childhood cancer, no relationships were found to link these tumors with oral clefts, or with prenatal exposure to viral infections (80,81).

Family Studies

Epidemiologic patterns of cancer suggest that the environment contributes much more to cancer risk than do genetic factors. Perhaps in the general run of patients, inherited susceptibility and interactions with environmental influences are too subtle or complex for detection by ordinary epidemiologic means. On occasion, when susceptibility is conspicuous, as in cancer-prone families, research opportunities are provided that may clarify the role of genetic and environmental factors in carcinogenesis. Studies on high-risk families are conducted jointly with the Clinical Epidemiology Branch, and with clinical and laboratory scientists at NIH and elsewhere. The patterns of familial cancer and the interdisciplinary approach were reviewed this year (82). The role of the research nurse was also described (83,84).

The development of an integrated manual and computerized record-keeping system provides a framework for an expanding data base that grew by over 200 new families in the past year, bringing the total to more than 1000 families. This system recently demonstrated its utility by enabling the rapid analysis of a complex set of data collected to assess the relationship

of autoimmunity to cancer. Thirty families identified with dermatitis herpetiformis (DH), 25 with gluten-sensitive enteropathy (GSE), and 30 with sicca syndrome are under evaluation. In a preliminary report of DH and GSE, family members were found to have an increased incidence of autoimmune disorders, but no excess of neoplasia (85).

Interdisciplinary studies of high-risk families continue to provide new insights into the mechanisms of host susceptibility to cancer. This research strategy is illustrated by the evaluation of familial melanoma and its relation to the dysplastic nevus syndrome, first described by Branch staff in 1978. Of 70 melanoma-prone families, nearly all have precursor moles. Reports this year helped to further characterize the mole syndrome (86), its occurrence in some patients with sporadic melanoma (87), and its treatment by topical chemotherapy (88). Over 350 members of 13 high-risk families have been examined, and biological specimens collected for a battery of laboratory studies, including immunologic investigations (89,90). Linkage analysis is planned using an extensive panel of genetic markers. Identification of this syndrome has enabled the diagnosis and removal of early-stage melanoma, and a comprehensive educational program has been developed for families and physicians.

Immunologic parameters have been evaluated in families susceptible to lymphoreticular neoplasms. The importance of long-term followup was illustrated by a family reported several years ago with sib aggregation of chronic lymphocytic leukemia and in vitro immune dysfunction. Recently, an offspring developed a related B-cell malignancy; laboratory studies now suggest a dominantly inherited deficiency of cellular immunity associated with a predisposition to lymphoproliferative neoplasms (91). Also reported was a family with Waldenstrom's macroglobulinemia occurring in a father and three offspring, along with autoimmune manifestations in the family (92). An immunogenetic mechanism was suggested by genetic linkage of cases to markers in the major histocompatibility locus. Associated with the HLA haplotype were B-cell alloantigens Ia-172 and Ia-350, previously reported in patients with the lymphoma-prone sicca syndrome. HLA typing of families prone to Hodgkin's disease suggested an excess of Bw-35 and Bw-37 (93), and recently a new locus was suggested within the major histocompability complex.

Studies were made of a family with an inborn cytogenetic abnormality (13:18 translocation). Acute leukemia and stomach cancer occurred among the carriers, and defective gonadal function was suggested by the presence of infertility in family members, along with ovarian cysts and teratomas. In collaboration with the Sloan-Kettering Institute, studies were carried out on families prone to colon cancer. An abnormality of actin cable structure was found in fibroblasts of patients with familial polyposis, but not in colon cancer-prone families without polyposis (95). In both types of families, there was a growth abnormality of colonic mucosa signaling an early mutational event (96). In other studies a predisposition to leukemia seemed related to the susceptibility of fibroblasts to SV40 infection and transformation (97-99). Studies are underway to examine DNA repair in various cancer-prone families. During the course of family

studies, biological specimens are placed in storage and utilized as new laboratory approaches are developed. Serum from 1300 family members and cultured skin fibroblasts from 2000 individuals are available for collaborative studies. Sera from one family helped establish that there was no linkage between variable and constant region allotypic markers on heavy chains (100).

Comprehensive reviews were prepared on the familial and genetic aspects of multiple myeloma and macroglobulinemia (101,102), and non-Hodgkin's lymphoma and mycosis fungoides (103,104). An excess of lymphoproliferative neoplasms was seen in family members of patients with mycosis fungoides (10). A review was made of congenital hemihypertrophy, which increases the risk of embryonal neoplasms involving the kidney, adrenal cortex, and liver (105). The association of polyposis and glioma (Turcot syndrome) was also reviewed (106), and comments prepared on the rarity of transplacental metastases of maternal cancer (107). One Branch member prepared a foreword to a monograph on Tumours of Early Life in Man and Animals (108).

Several studies were conducted with the NIH Clinical Center staff. Two patients with Charcot-Marie-Tooth disease subsequently developed melanoma, suggesting a shared neural crest defect or genetic linkage (109). An outbreak of varicella-zoster infection was investigated to clarify the mechanisms of infectious spread (110). A followup is being prepared on 35 families prone to sarcomas and other neoplasms, to better delineate the syndrome of tumors originally described by Branch staff and to search for susceptibility mechanisms.

Infectious Agents

Viruses have not been causally tied to the origins of any human cancer, but candidate agents are suspected for cervical cancer (herpes virus type 2), Burkitt's lymphoma and nasopharyngeal carcinoma (Epstein-Barr virus), and liver carcinoma (hepatitis-B). This year one staff member reported on clinical and etiologic investigations of African BL, which is thought to be related to the combination of EBV and malarial infection in young children (111-115). The incidence and timing of EBV infection in African and American children were studied (116). In African children the patterns of malaria were examined to see if its epidemiologic behavior is consistent with that of BL (117). Serial studies of EBV in patients with BL showed no change in antibody after late relapse, suggesting that the presence of tumor is not responsible for the high titer seen in BL patients. The biological effects of malaria on infants, and relationships to EBV titers are also being evaluated. The role of chromosome abnormalities, including the 14q+ marker, and HLA types is being examined in patients with BL.

EBV is also among the risk factors being evaluated to explain the high rates of nasopharyngeal cancer in Alaskan natives. A study of childhood cancer with epidemiologists at Oxford University revealed no association with varicella, despite previous reports to the contrary (118). The role of parasites, including malaria, clonorchiasis, and schistosomiasis in cancer etiology was reviewed (119).

Immunoepidemiology

In addition to the evaluation of immunosuppressive drugs and immune defects in high-risk families (described above), various projects were undertaken this year to clarify the role of immunologic alterations in carcinogenesis. In collaboration with the University of Minnesota, a registry of cancers occurring in patients with primary immunodeficiency syndromes has been maintained. Now totaling 291 cases, lymphomas continue to predominate, similar to the experience of transplant recipients. Among the carcinomas, stomach cancer is most common, especially in patients with chronic variable immunodeficiency.

An updated analysis of 16,000 renal transplant recipients reported to the American College of Surgeons has revealed a 32-fold excess of non-Hodgkin's lymphoma, mainly histiocytic lymphoma (about 150 times the expected rate). The risk of other cancers was increased two-fold, but did not affect all tumors across-the-board, as might be expected by the immunosurveillance hypothesis. Instead, the excess was limited to particular forms of cancer, including hepatobiliary neoplasms, lung adenocarcinoma, urinary tract tumors, soft-tissue sarcomas, melanomas, and squamous cell carcinomas of the skin. Although oncogenic viruses may be involved in post-transplant lymphoma, there was no evidence of time-space clustering or a higher incidence in transplant recipients having contact with lymphoma patients in the induction period (120). These findings do not exclude a role for viruses in post-transplant lymphomas, since malignant transformation from a latent viral infection would not be reflected in clustering. A collaborative arrangement has now been established with the End Stage Renal Disease Program of the Health Care Financing Administration to evaluate cancer risks among transplant recipients and dialysis patients.

Various disorders with secondary or acquired immunologic defects have been associated with an excess risk of cancer, primarily lymphomas, and follow-up surveys are underway among patients with sicca syndrome, leprosy, gluten-sensitive enteropathy, sarcoidosis, and other conditions. Planning was completed with the Veterans Administration for studies relating several immunological disorders to cancer risk. Nearing completion is a follow-up study to evaluate the fate of 3000 former employees of Ft. Detrick, Maryland, who were "hyperimmunized" by repeated vaccination.

Veterinary Studies

These studies are based mainly on the NCI-supported Veterinary Medical Data Program operated by a consortium of 20 North American veterinary university teaching hospitals. By epidemiologic comparisons to human cancer, studies in domestic animals are designed to clarify risk factors in human cancer and related diseases, uncover animal models (e.g., breeds) that may be useful in further research, and identify sentinels that may act as early predictors of environmental hazards. This year a study of urethral cancer in dogs (121) revealed a pattern similar to canine bladder cancer. The apparent sparing effect in male dogs was attributed to the presence of resting prostatic secretion in the urethra between micturitions.

In another study, the frequency of canine bladder cancer from 11 U.S. counties was strongly correlated with the amount of industrial activity in the same area. In those counties a similar correlation was found for human bladder cancer, suggesting that pets and owners may be affected by the same bladder carcinogens (122). Geographic patterns were also examined for canine heartworm infection (Dirofilaria immitis) which prevails in areas of the U.S. with a warm and wet climate but is also now seen in northern climates (123).

Hormonal relationships were studied in dogs with perianal gland neoplasms (124), and hypothyroidism (125). Perianal gland tumors were effectively treated by castration alone and often associated with interstitial cell tumors of the testis. Hypothyroidism was excessive among spayed females compared to sexually intact female dogs. Review of the features of mammary carcinoma in cats (126) showed that spayed animals had 0.6 the risk of sexually intact females, but other hormonal influences were not evident, suggesting that the cat is a poor model for the human disease.

Several congenital and developmental defects in animals were studied. There was a predisposition to elbow dysplasia among large and giant breeds (127) suggesting that rapid growth or weight are involved in this common syndrome. A study of hip dysplasia in domestic cats revealed a very low hospital prevalence (128). Diaphragmatic hernia in dogs was found most often at the pericardial site and was associated with cardiac defects in many cases (129). A predisposition to congenital deafness in dogs was identified in the Dalmatian and six other breeds, many of which are also prone to pigment abnormalities of the coat and eye (130).

Progress in veterinary cancer studies was reviewed by comparing the epidemiologic features of canine, feline, and human cancers at ten body sites (131), and by a critique of the Veterinary Medical Data Program (132).

Methodologic Studies

Several Branch members contributed to the adaptation and development of statistical methods useful in epidemiologic studies. A text was published which featured a library of programs for epidemiologic analysis using a programmable calculator (133). One Branch member coordinated an issue of Environmental Health Perspectives which consisted of a series of papers on biostatistical methods in cancer research in the U.S. and Japan (134,135).

Research continued on methods of analysis of case-control data. A link for tests of hypotheses between the logistic model and the more traditional Mantel-Haenszel method was shown (136), and a simulation study suggested that two proposed approximations to the exact conditional likelihood for matched case-control data can lead to poor relative risk estimates (137). The use of Miettinen's confounder score was shown to be at times inappropriate or else may lead to a conservative bias in the

estimated relative risk (138). Graphical aides were prepared to illustrate the relative efficiency gains possible in estimating relative risks by selecting the sample size of the control group two to five times larger than the case group (139). A note was prepared clarifying the difference between the statistical concept of interaction and the epidemiologic concept of synergy (140).

Several studies were conducted on the statistical analysis of cohort data. One report presented an alternate method for analysis by the Cox proportional hazards failure time model (141). Reports were prepared proposing a simple variance approximation for the Mantel-Haenszel chi-square statistic and a conversion factor for obtaining standardized mortality ratios (SMRs) from proportionate mortality studies (142). Regression methods for use with disease rates were refined, extended and liberalized (143). Methodologic issues were also explored with respect to descriptive and correlational studies, especially using the county-by-county mortality resource (144-147).

Work continued into the development and accessibility of the Branch computer program library. For case-control data, SAS pre-programmed sub-routines have been written to estimate and test relative risks and to facilitate logistic modelling (149,150), with details of these programs presented to NIH staff via seminars and individual consultation. For matched studies a general program for multivariate analysis was developed based on an exact conditional likelihood (151). A guide to sample size requirements for use in familial studies of cancer was prepared (152). A seminar series for NIH staff was given on statistical methodology used in genetic and family studies.

Reviews

The Branch continued to provide comprehensive and critical reviews of etiologic factors in cancer. One staff member served as co-editor of a comprehensive text on the epidemiology and prevention of cancer (153). This year reviews were prepared on several cancers including the lung (154-156), pancreas (157), biliary tract (158), multiple myeloma (101,102), non-Hodgkin's lymphoma (103,104), soft-tissue sarcomas (159), and bone cancer (160). The epidemiologic evidence for environmental carcinogenesis (161), genetic susceptibility (162), and multi-stage mechanisms (163) was reviewed. Several environmental hazards were considered in detail, including ionizing radiation (49-56), occupational exposures (24), hormones and other drugs (62-66), parasites (119), and food additives (78).

OTHER ACTIVITIES

The Branch continued to provide a liaison for epidemiologic research in the National Cancer Program and for environmental cancer studies being conducted in various agencies in the federal government. A great deal of advice and support is given to clinicians, experimentalists, and public health officials. Members serve on the editorial board of various journals and on advisory groups and committees connected with cancer centers,

several federal and state agencies, and other national and international activities. Several meetings and projects this year were related to bi-national agreements with the Soviet Union, Japan, Italy, and the People's Republic of China. At times the Branch became embroiled in controversial issues and debates (e.g., fluoridation and cancer, low-level radiation, occupational hazards, artificial sweeteners) and in policies and regulations that pose obstacles to epidemiologic research.

Special efforts were made this year to identify and utilize epidemiologic resources best available at the national level. Initiatives were taken to stimulate cooperative arrangements with several government agencies in charge of routinely collected data resources that can be utilized for epidemiologic studies (e.g., Social Security Administration). Another important activity of the Branch is the on-the-job training of staff at the post-doctoral level, the supervision of elective periods for medical students, field research opportunities for doctoral candidates at schools of public health, and the assignment of visiting scientists with limited experience in epidemiology. Although the Branch encourages an atmosphere of academic freedom in the development of new ideas and approaches, these are met with criticial review and evaluation through several mechanisms--frequent section and Branch meetings, close contacts with support service and collaborating groups, various formal review mechanisms, several working groups (e.g., data resources, radiation studies, family studies, drug studies), interagency committees, the Clinical Center review committee involving clinical investigations, careful scrutiny of questionnaires and their clearance through governmental channels, ad hoc external review groups for major studies (e.g., national bladder cancer project), an NIH coordinating epidemiology committee, and a variety of committees that oversee Institute activities, including the Board of Scientific Counselors of the Division of Cancer Cause and Prevention.

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This committee advises the Director of the Division of Cancer Cause and Prevention on a wide variety of matters having to do with the progress of the programs of the Division. This includes evaluation of productivity and performance of staff scientists through periodic site visits to intramural laboratories; evaluation of the collaborative and resource activities of the Division; and evaluation and advice on the future course of the Division's programs. The advisory role of the Board of Scientific Counselors is scientific and does not include deliberation on matters of public policy. Areas of expertise include cellular and molecular carcinogenesis, molecular biology, epidemiology, immunology, experimental pathology, cytogenetics, and viral oncology.

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Contracts Review Branch
Division of Extramural Activites
National Cancer Institute

FIELD STUDIES AND STATISTICS PROGRAM REVIEW GROUP

The FS&S Program Review Group advises and assists the Associate Director for Field Studies and Statistics in the management of the Program. The Group recommends new programs to the Associate Director for implementation. The Group advises on the issuance and scope of all RFP's and new research projects in FS&S. It provides technical review of all resource and support contracts for award and renewal with the help of ad hoc committees who screen for acceptability proposals received in response to published RFP's.

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NATIONAL BLADDER CANCER STUDY

This Group advises the NCI on the design, execution, analysis and interpretation of the National Bladder Cancer Study. This study was appropriated specifically by Congress in response to the question of risk for bladder cancer among users of saccharin. The Group reviews and specifically approves reports generated by the study.

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FIELD STUDIES AND STATISTICS PROGRAM

FY 1980 Budget

	NUMBER OF BUDGETED POSITIONS	INTRAMURAL $ Millions	CONTRACTS $ Millions	GRANTS Millions	TOTAL
Office of the Associate Director	4	0.3			0.3
Biometry Branch	64	3.1	3.9	0.7	17.0
SEER Program			9.4 } 13.3		
Clinical Epidemiology Branch	12	0.7	0.1		0.8
Environmental Epidemiology Branch	45	2.2	9.4		11.6
TOTAL	125	6.3	22.8	0.7	29.7

FY 1981 Budget (Projected)

Office of the Associate Director	6	0.5			0.5
Biometry Branch	62	3.6	13.0	0.4	17.0
Clinical Epidemiology Branch	12	0.7	0.4		1.1
Environmental Epidemiology Branch	46	3.0	10.3		13.3
TOTAL	126	7.8	23.7	0.4	31.9

CONTRACTS
SEER PROGRAM, BIOMETRY BRANCH

CONTRACT	TITLE
California State Department of Health (NO1-CP-81018)	Surveillance, Epidemiology and End Results Reporting (SEER) Program
California, University of (NO1-CP-43383)	Tumor Registry Training Program
Commonwealth of Puerto Rico (NO1-CP-43386)	SEER Program
Connecticut State Department of Health (NO1-CP-61002)	SEER Program
Emory University (NO1-Cp-61027)	SEER Program
Fred Hutchinson Cancer Research Center (NO1-CP-61059)	SEER Program
Geomet, Inc. (NO1-CP-81019)	Computer Support for SEER Program
Hawaii, Research Corp. of Univ. of (NO1-CP-53511)	SEER Program
Iowa, University of (NO1-Cp-43200)	SEER Program
Michigan Cancer Foundation (NO1-CP-61028)	SEER Program
New Mexico, University of (NO1-CP-33344)	SEER Program
Triton Corp. (NO1-CP-91032)	Computer Support for Non-melanoma Skin Cancer Study
Utah, University of (NO1-CP-43382)	SEER Program
Yale University (NO1-CP-33234)	SEER Program

CONTRACTS
BIOMETRY BRANCH

CONTRACT	TITLE
Bergen, University of (Norway) (NO1-CP-91043)	Analyses of Prospective Studies on Diet, Cancer, and Other Diseases in Selected Migrant Populations (Norwegian)
California State Department of Health (NO1-CP-01000)	Study of Morbidity in Childhood Cancer Survivors
Fundacion Para la Educacion Superior (NO1-CP-33286)	Cancer Morbidity Study in Cancer
Health Insurance Plan of Greater New York (NO1-CP-43278)	Evaluation of Periodic Breast Cancer Screening by Mammography
Information Management Services, Inc. (NO1-CP-01025)	Computer Services
International Agency for Research on Cancer (NO1-CP-71015)	Mortality from Cancer in Relation to Occupation and Social Class
Iowa, University of (NO1-CP-01001)	Study of Morbidity in Childhood Cancer Survivors
Israel Center for Registration of Cancer and Allied Diseases (NO1-CP-33351)	Cancer Incidence in Israel
Kansas, University of (NO1-CP-01036)	Study of Morbidity in Childhood Cancer Survivors
Kuakini Medical Center (NO1-CP-61060)	Study of Cancer Among Japanese Migrants
Minnesota, University of (NO1-CP-91021)	Analyses of Prospective Studies on Diet, Cancer, and Other Diseases in Selected Migrant Populations (Norwegian)
Southern California, University of (NO1-CP-91027)	Study of Cancer Incidence in the South Pacific
Texas, University of, Cancer Center (NO1-CP-01035)	Study of Morbidity in Childhood Cancer Survivors
Yale University School of Medicine (NO1-CP-01002)	Study of Morbidity in Childhood Cancer Survivors

CONTRACTS
CLINICAL EPIDEMIOLOGY BRANCH

CONTRACT	TITLE
Atomic Energy of Canada, Ltd. (NO1-CP-81102)	*In Vitro* Radiosensitivity and DNA Repair in Genetic Syndromes and Families at High Risk of Malignancy
Biotech Research Laboratories, Inc. (NO1-CP-61011)	Cytogenetic Evaluation of High Risk Cancer Families

CONTRACTS
ENVIRONMENTAL EPIDEMIOLOGY BRANCH

CONTRACT	TITLE
Associated Veterinary Medical Data Program Participants, Inc. (NO1-CP-1056)	Animal Morbidity/Mortality Survey of Colleges of Veterinary Medicine
Bureau of the Census (YO1-CP-7051)	County Population Estimates by Age, Race and Sex for the 1970's
Center for Disease Control (YO1-CP-00500)	Epidemiologic Studies of Cancer in Alaskan Natives
Chaim-Sheba Medical Center (NO1-CP-01042)	Radiation Risk Estimation in Israeli Children Irradiated for Tinea Capitis
Children's Hospital, Philadelphia NO1-CP-91049	Late Effects of Treatment for Cancer in Childhood
Duke University (NO1-CP-53890)	Histocompatability Testing Center
E.I. DuPont de Nemours Co. (NO1-CP-01038)	Study of Bladder Cancer Screening Program
Florida, University of (NO1-CP-01016)	Bovine Leukosis Survey of Florida
George Washington University (NO1-CP-81051)	Study of Ovarian Cancer in Greater Washington, D. C.
Harvard University (NO1-CP-81058)	Followup of Fluoroscopically Examined Tuberculosis Patients in Relation to Incidence of Cancer

CONTRACT	TITLE
Hawaii, University of (NO1-CP-71006)	Occupational Cancer Risk in Hawaii
Kaiser Foundation Research Institute, Oakland, Calif. (NO-CP-81047)	Studies on Environmental Cancer Utilizing a Pre-Paid Health Plan
Kaiser Foundation Research Institute, Portland, Oregon (NO1-CP-81046)	Studies on Environmental Cancer Utilizing a Pre-Paid Health Plan
Kaiser Foundation Research Institute, Oakland, Calif. (NO1-CP-91028)	Study of Relationship Between Conjugated Estrogen and Risk of Breast Cancer Among Oopherectomized Women
Lehigh University (NO1-CP-81038)	Epidemiologic Study of Lung Cancer in Communities With Non-ferrous Smelters
Litton Bionetics (NO1-CP-61016)	Immunologic Assessment of High Risk Cancer Families
Louisiana State University (NO1-CP-91023)	Cancer in Southern Louisiana: A Case-Control Study of Lung, Pancreas, and Stomach Cancers
Mayo Foundation (NO1-CP-01057)	Leukemia Following Chemotherapy for Ovarian Cancer
Meloy Laboratories (NO1-CP-9100)	Skin Fibroblast Repository for Patients at High Risk of Cancer
Memorial Hospital (NO1-CP-1050)	Risk Factor in Colo-rectal Cancer
Miami, University of (NO1-CP-81000)	A Case-Control Study of Etiologic Factors for Lung Cancer in Northeast Florida
Minnesota, University of (NO1-CP-43384)	Immunodeficiency--Cancer Registry
Minnesota, University of (NO1-CP-91014)	Long-Term Mortality Study of Minnesota Iron-Ore Miners
Minnesota, University of (NO1-CP-01030)	Risk of Cancer in X-Ray Technologists
Minnesota, University of (NO1-CP-01033)	Study of Environmental Factors in Leukemia and Non-Hodgkin's Lymphoma in Rural Areas.

CONTRACT	TITLE
Minnesota, University of (NO1-CP-01048)	Renal Cell Carcinoma Associated with Chromosomal Translocation
National Academy of Sciences (NO1-CP-01012)	Epidemiological Studies of Cancer Among A-Bomb Survivors
National Academy of Sciences (NO1-CP-53573)	Epidemiologic Studies in Etiology of Cancer in Veterans
National Center for Health Stats. (YO1-CP-80503)	Abstracting Death Certificate Information
National Oceanic and Atmosph. Admin. (YO1-CP-80506)	Automated Graphics Support
Naval Medical Research Institute (YO1-CP-00502)	Immunologic Immunogenetics Determinants of High Risk Cancer Families
New Jersey State Department of Hlth (NO1-CP-61031)	Etiologic Studies of Cancer in New Jersey
New Jersey State Environmental Protection Admin. (NO1-CP-91048)	Characterization of Industrial Emissions in N.J. with Emphasis on Bladder Cancer
ORI, Inc. (NO1-CP-01054)	Computer Support for Environmental Epidemiology
Pennsylvania, University of (NO1-CP-91047)	Special Projects in Hereditary Cutaneous Melanoma
Systemedics, Inc. (NO1-CP-01043)	Support Services for Radiation Studies
Texas, University of M.D. Anderson Hospital (NO1-CP-01047)	Study of Iatrogenic Cancer and Radiation Dosimetry
Texas, University of M.D. Anderson Hospital (NO1-CP-01051)	Family Study in Melanoma
Texas Health Science Ctr., University of (NO1-CP-91037)	Epidemiology of Primary Liver Cancer in Selected Counties of Texas
Texas Health Science Ctr., University of (NO1-CP- 91025)	Etiologic Study of Respiratory Cancer in Coastal Texas

CONTRACT	TITLE
Westat, Inc. (NO1-CP-01011)	Support Services of Radiation Studies
Westat, Inc. (NO1-CP-61034)	Support Services for Field Studies
Westat, Inc. (NO1-CP-81017)	Role of Saccharin in Bladder Cancer
Westat, Inc. (NO1-CP-91034)	Support Services for Occupational Studies
Westat, Inc. (NO1-CP-01044)	Support Services for Epidemiologic Studies
Yale University (NO1-CP-01029)	Risk of Cancer Following Multiple Chest Fluoroscopies for Tuberculosis in Conn.

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